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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,207	02/13/2006	Mitsuo Oshimura	081356-0239	1647

22428 7590 06/18/2009

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
06/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,207	OSHIMURA ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20-23,26-28,33,49-51 and 3746* is/are pending in the application.

4a) Of the above claim(s) *1-17,23 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20-22,26-28,33,37-46,49 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on June 27, 2008 is acknowledged. Applicant has elected the invention of Group III, claim(s) 18-23, 26-28, 33 and 37-48, drawn to a method of making a human artificial chromosome vector comprising obtaining cells that retain human chromosome 21 and deleting a distal region of the long or short arm of the human chromosome 21.

Within Group III, Applicant has elected the deletion site species "AL163204", which is located in the long arm of human chromosome 21.

Amendments

In the reply filed March 25, 2009, Applicant has cancelled Claims 19, 24-25, 29-32, 34-36 and 47-48, withdrawn Claims 1-17 and 23, amended Claims 18, 20-23, 26-28, 33, 37, 40, 42 and 45, and added new claims, Claims 49-51.

Claims 1-17, 23 and 51 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 18, 20-22, 26-28, 33, 37-46 and 49-50 are under consideration.

1. **The prior objection to Claims 18-22, 26-28, 33 and 37-46 is withdrawn** in light of Applicant's amendment to the claims to delete recitation of non-elected subject matter, specifically "human chromosome 14".

Priority

This application is a 371 of PCT/JP03/12734, filed on October 3, 2003. Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Certified copies, but not English translations, of PCT/JP03/12734, filed on October 3, 2003 and JP2002-202853 filed on October 4, 2002 have been filed with the instant application.

Accordingly, the effective priority date of the instant application is granted as October 4, 2002.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the March 25, 2009 response will be addressed to the extent that they apply to current rejection(s).

Specification

2. **The prior objection to the disclosure is withdrawn** in light of Applicant's deletion of embedded hyperlink and/or other form of browser-executable code.

Claim Objections

3. **The prior objection to Claims 22, 26-28 and 33 under 37 CFR 1.75(c)** as being in improper form **is withdrawn** in light of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 112

4. **The prior rejection of Claims 19-20 under 35 U.S.C. 112, second paragraph, is withdrawn** in light of Applicant's cancellation of the term "high…efficiency".

5. **The prior rejection of Claim 20 under 35 U.S.C. 112, second paragraph, is withdrawn** in light of Applicant's amendment to the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **Claims 41 and 46 stand rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for methods for producing a mouse embryonic stem (ES) cell comprising a modified foreign chromosome or fragments thereof, does not reasonably provide enablement for methods for producing embryonic stem (ES) cells from an enormous genus of biologically distinct organisms comprising modified foreign chromosomes or fragments thereof.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not

disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claims are broad for encompassing about 1,000,000 species of animals (waynesword.palomar.edu/trfeb98.htm, last visited November 26, 2007). Mammalian subjects reasonably encompasses some 5,500 species (including humans), distributed in about 1,200 genera, 152 families and up to 46 orders (en.wikipedia.org/wiki/Mammal, last visited March 21, 2007), wherein the art teaches that there are approximately 4,000 rodent species, divided into three major groups or sub-orders, Sciuromorpha, Myomorpha and Hystricomorpha, and more than 30 families. The diversity of instantly claimed rodent genus reasonably encompasses, for example, squirrels, chipmunks, beavers, woodchucks, prairie dogs, hamsters, lemmings, voles, porcupines, capybaras, agoutis, chinchilla, as well as many species whose common names include the term "rat" (columbia.thefreedictionary.com/rodent).

The claimed invention is directed to methods for producing a mouse embryonic stem (ES) cell comprising a modified foreign chromosome or a fragment thereof, comprising preparing a microcell comprising a foreign chromosome or a fragment thereof, and transferring said foreign chromosome or a fragment thereof into a cell with high homologous recombination efficiency through its fusion with said microcell, in said cell with high homologous recombination efficiency, inserting a targeting vector by homologous recombination into a desired site of said foreign chromosome or fragment thereof and a desired site of a chromosome derived from said cell with high homologous recombination efficiency, thereby marking the desired site; and causing the deletion and/or translocation to occur at the marked site of the foreign chromosome or fragment thereof.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The inventive concept in the instant application is the use of mouse embryonic stem (ES) cells (pg 18, lines 4-5; pg 128, Example 24), wherein such ES cells may then be used to generate chimeric mice to establish germline transmission of the telomere-truncated human chromosome fragment (pg 27, ¶3).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The claimed invention is directed to embryonic stem (ES) cells that comprise modified foreign chromosomes or fragments thereof. However, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith et al, J. Mol. Med., 1997, p. 214, Summary). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith et al supports this observation as they discuss the historical perspective of mouse ES cells as follows: "The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of

these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins et al (Journal of Clinical Investigation, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (pg 1558, col. 2, ¶1). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), the state of the art supports that only mouse ES cells were available.

This is further supported by Pera et al (Journal of Cell Science 113:5-10, 2000) who present the generic criteria for pluripotent ES or EG cells and state that, "Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously." (see pg 6, col. 2, last ¶)

The physiological art is recognized as unpredictable. (MPEP §2164.03) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. The art teaches that the properties of embryonic stem cells are highly species specific and that processes developed using a mouse ES cell cannot be generically applied to all ES cells. In particular, the art recognizes that ES cells isolated from different species exhibit significantly different properties. Wheeler (US Patent No. 5,942,435) describes many problems encountered in extending successes obtained with mouse ES cells to other mammalian species. For example, Wheeler teaches that attempts to establish useful stem cells from pigs and sheep produced disappointing results (col. 2, ¶3; col. 3, ¶5); and teaches that a problem "in extrapolating from mice to ungulates, such as swine, is that exactly analogous stages do not exist in the embryos of mice and ungulates..." (col. 4, ¶2). Thus, establishing ES cell lines from other species of mammals or animals having properties that are analogous to the mouse ES cells used in the methods of the instant application is highly unpredictable. It is noted that the unpredictability of a particular area may alone provide reasonbale doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Accordingly, in view of the state of the art of ES cells, and the lack of guidance or teachings provided by the specification for the availability of ES cells from species other than mouse, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a method comprising the use of a mouse embryonic stem (ES) cell comprising a modified foreign chromosome or fragments thereof, is proper.

Response to Arguments

Applicant argues that:

a) at the time the present invention was made, embryonic stem cell lines from many sources were available, including mouse ES, human ES, cynomolgus monkey ES and rhesus monkey ES [0477-478]. For example, see Thomson et al., Science 282: 1145-47 (1998) (Exhibit A to this response). Thus, a skilled person would have had full access to ES cells from a variety of organisms; and

b) Applicants have amply described their invention in terms that enable the skilled person to implement the claimed methodology, in keeping with relevant M.P.E.P. guidelines, to the transfer of foreign DNA from a HAC vector to recipient cells, e.g. CHO cells, pluripotent cells, chicken cell lines, human cell clones, etc…

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), the Examiner notes that Exhibit A was not provided in the papers with Applicant's response. At issue is that the claims reasonably embrace an enormous genus of animal cells, e.g. insect, bird, reptile, amphibian and mammal. The presence of ES obtained from mouse, human, cynomolgus monkey and rhesus monkey [four animal species] at the time of the invention is not commensurate in scope to the real world genus of animals comprising about 1,000,000 animal species. The art teaches that the properties of embryonic stem cells are highly species specific and that processes developed using a mouse ES cell cannot be generically applied to all ES cells. In particular, the art recognizes that ES cells isolated from different species exhibit significantly different properties. Thus, establishing ES cell lines from other 99,996 animal species having properties that are analogous to the mouse ES cells used in the methods of the instant application is highly unpredictable. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).

With respect to b), the Examiner has not rejected the use of CHO cells, pluripotent cells, chicken cell lines, human cell clones, etc… for the particular invention. Again, Applicant's attention is directed to the broadly claimed genus of animal ES cells for which the art has **simply not yet identified** the remaining 99,996 distinctly different animal ES cells reasonably encompassed by the claim. For example, Applicant provides no evidence of record that embryonic stem cells have been isolated in a multitude of animals sufficiently representing the claimed approximately 1,000,000 animal species, e.g. fruit flies, frogs, giraffes, capybaras, koalas, turkeys, lizards and turtles, such that when said ES cell is transfected with the inventive artificial chromosome, said cell is capable of transmitting the artificial chromosome to the next generation (offspring of transgenic parent organism) as disclosed in the specification [0103].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. **The prior rejection of Claims 18-21, 26-27, 33 and 37-46 under 35 U.S.C. 103(a)** as being unpatentable over Kuroiwa et al (NAR 26(14):3447-3448, 1998; *of record in IDS) in

view of Kuroiwa et al (Nature Biotechnol. 18:1086-1090, 2000; *of record in IDS) and Tomizuka et al (Nature Genetics 16:133-143, 1997; *of record in specification) **is withdrawn** in light of Applicant's amendment to the claims specifying the deletion of a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21, a limitation that neither Kuroiwa et al ('98, '00) nor Tomizuka et al teach.

8. **The prior rejection of Claims 22 and 28 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Kuroiwa et al (1998; *of record in IDS) in view of Kuroiwa et al (2000; *of record in IDS) and Tomizuka et al (1997; *of record in specification), as applied to claims 18-21, 26-27, 33 and 37-46 above, and in further view of Hattori et al (Nature 405(6784):311-319, 2000) **is withdrawn** for reasons discussed above.

9. **Claims 18, 20-21, 26-27, 33 and 37-46 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Kuroiwa et al (1998; *of record in IDS) in view of Kuroiwa et al (2000; *of record in IDS), Tomizuka et al (1997; *of record in specification) and Saffery et al (J. Gene Med. 4:5-13, 2002; *of record in IDS).

Determining the scope and contents of the prior art.

Kuroiwa et al teach a method for producing a human artificial chromosome vector and a method of introducing foreign DNA into a recipient cell, the methods comprising the step of obtaining donor cells that retain human chromosome 22, deleting a distal region of the long arm and/or a distal region of the short arm of the human chromosome 22, wherein the deletion step is by substitution with an artificial telomere sequence, wherein the cells that retain human chromosome 22 are chicken DT40 cells that have a high homologous recombination rate (pg 3447, Figure 1).

Kuroiwa et al do not teach the step of inserting a recognition site for a site-specific recombination enzyme into a proximal region of the long arm and/or a proximal region of the short arm of the human chromosome. However, at the time of the invention, Kuroiwa et al (2000) taught a method for producing a human artificial chromosome vector, the method comprising the combination of a chromosome comprising site-specific, Cre/loxP-mediated, homologous recombination and telomere-directed chromosome truncation in homologous recombination-proficient chicken DT40 cells, and the step of inserting foreign DNA into the human chromosome in the presence of a site-specific recombination enzyme. The site-specific recombination recognition site, loxP, was integrated into a locus of the human chromosome.

Kuroiwa et al teach the step of preparing microcells from the donor cells that retain the human chromosome and fusing the microcells comprising a human chromosomal vector to a recipient cell that is a mouse embryonic stem cell, wherein those of ordinary skill in the art recognize ES cells to reasonably embrace mesenchymal and tissue stem/precursor cells given their developmental totipotentcy, the step of selecting cells expressing the foreign DNA among the fused recipient cells, and the step of confirming the introduction of the foreign DNA into the fused recipient cells, e.g. by FISH analysis. Kuroiwa et al suggest that various human chromosomal regions defined by loxP-integration and telomere-truncation sites can be cloned by this method. The cloning capacity is at least 10 Mb greater than in conventional cloning methods (pg 1086; pg 1087, col. 1, Figure 1; pg 1088, Figure 2).

Kuroiwa et al ('98, '00) do not teach the human chromosome to be chromosome 21. However, at the time of the invention, Tomizuka et al taught a method of producing a human artificial chromosome vector, a method of introducing foreign DNA into a recipient cell, and producing a cell that expresses foreign DNA, the methods comprising the use of a library of human-mouse A9 monochromosomal hybrids that retain human chromosomes, wherein each human chromosome is randomly tagged with a selectable marker suitable for use in mouse ES cells. Tomizuka et al teach the step of obtaining cells that retain human chromosome 14 or 22, the step of preparing microcells from the donor cells that retain the human chromosome and fusing the microcells comprising a human chromosomal vector to a recipient cell that is a mouse embryonic stem cell, wherein those of ordinary skill in the art recognize ES cells to reasonably embrace mesenchymal and tissue stem/precursor cells given their developmental totipotentcy, the step of selecting cells expressing the foreign DNA, e.g. G418 resistance, among the fused recipient cells, and the step of confirming the introduction of the foreign DNA into the fused recipient cells, e.g. by FISH analysis (pg 133, col. 2; pg 134, col. 1, Figures 1 and 2). Tomizuka et al teach that using the Cre-loxP system, replacing a specific mouse chromosomal region with the corresponding human chromosomal fragment will be possible (pg 140, col. 2, ¶2). Tomizuka et al teach that efforts to repeat the method using human Chromosome 21 are underway to investigate various aspects of Down's syndrome (pg 140, col. 1, ¶2).

Neither Kuroiwa et al ('98, '00) nor Tomizuka et al teach the deletion of a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21. However, at the time of the invention, Saffery et al taught that the strategies to produce a functional human artificial chromosome comprise the deletion of a distal region within the centromere-proximal region of the long arm and/or a distal region within the centromere-proximal region of the short arm of the human chromosome (pg 7, Figure 1; pg 9, Figure 2), whereupon the telomeric region either juxtaposes or is in close proximity to the α-satellite-based centromere.

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology and the creation of transgenic cells comprising artificial/recombinant human chromosomes. Therefore, the level of ordinary skill in this art is high. The technology to shorten a chromosome by introducing a cloned telomere sequence by homologous recombination (telomere truncation) has been practiced in the art since 1992 (Specification, pg 21).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to combine the instantly recited method steps into a single method for producing a human artificial chromosome vector, introducing foreign DNA into a recipient cell, and producing a cell that expresses foreign DNA with a reasonable expectation of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. It is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose (as well as to use such a composition for that purpose). The idea for combining them flows logically from their having been used individually in the prior art, and from them being recognized in the prior art as useful for the same purpose. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients. *In re Kerkhoven*, 626 F.2d 846, 850, 205 U.S.P.Q. 1069 (CCpA 1980), *In re Sussman*, 1943 C.D. 518; *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423,426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). In the instant case, all such method steps were practiced in smaller combinations by the ordinary artisan in methods for producing a human artificial chromosome vector, introducing foreign DNA into a recipient cell, and producing a cell that expresses foreign DNA. An artisan would be motivated to combine the instantly recited method steps into a single method for producing a human artificial chromosome vector, introducing foreign DNA into a recipient cell, and producing a cell that expresses foreign DNA because Kuroiwa et al (2000) teach the successful combination of site-specific, homologous recombination and telomere-directed chromosome truncation in homologous recombination-proficient chicken DT40 cells.

It also would have been obvious to one of ordinary skill in the art to substitute a first human chromosome as taught by Kuroiwa et al (1998, 2000) and/or Tomizuka et al with a second human chromosome that is chromosome 21 with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P.

§2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)". When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, those of ordinary skill in the art recognized that the human genome comprises a finite set of chromosomes, and Tomizuka et al teach that construction of human artificial chromosome vectors comprising human chromosome 21 is of biological interest, e.g. the study of Down's Syndrome.

It also would have been obvious to modify the method for producing a human artificial chromosome vector as taught by Kuroiwa et al (1998, 2000) and/or Tomizuka et al to comprise the step of deleting a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21 with a reasonable expectation of success because the prior art contained a "base" product, specifically a human chromosome, more specifically hChr21, upon which the prior art may apply a known technique (Kuriowa et al, '98, '00; Saffery et al) to engineer said hChr21 into an artificial mini-chromosome vector, the motivation being that Saffery et al taught that such centromere-proximal deletions is a routine design when engineering human mini-chromosome vectors, the 21q11 and 21p11 regions are art-recognized centromere-proximal regions, whereupon such would have yielded predictable results and resulted in an improved hChr21 artificial mini-chromosome having improved mitotic stability.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that:

a) the prior art of record evinces no recognition that the category of human chromosomes would be fungible in this context, such that chromosome 21 and the disclosed chromosome were interchangeable; and

b) A HAC vector, as recited, can be transferred to human normal fibroblasts and to human normal somatic cells other than fibroblasts. Such a HAC vectors also is retained stably, for example, in chicken cell lines and human cell clones (Examples 4 and 18) and in human stem

cells (Examples 2 1-22), *inter alia*. These results are unexpected because, at the time the present invention was made, the prior art taught that human artificial chromosomes were not stable in mammalian cells. See Mills et al (1999) (Exhibit B) and Heller et al (1996) (Exhibit C). Accordingly, there was a clear prejudice in the art against the transfer of artificial chromosomes into mammalian cells, underscoring the surprising and, hence, patentable aspects of Applicants' claimed invention.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), Kuroiwa ('98) successfully demonstrate the substitution of human chromosome 22 (hChr22) for hChr3 in a method for producing an artificial human chromosome vector, achieving high efficiency of targeted truncation and suggest that this technology is useful for detailed gene mapping by functional assays hChrs (pg 3448, col. 1). Kuroiwa ('00) teach that the successful strategy to clone, stabilize and functionally analyze greater than megabase-sized defined human chromosomal regions as applied to hChr22 was also applied to hChr2 (pg 1086), and suggest that hChrs previously difficult to clone by conventional cloning methods may be cloned and stabilized as per their method (pg 1087, col. 2). Tomizuka ('97) taught a successful method of producing hChr 2, 14 and 22 fragments and suggest the application of said method towards hChr21. Thus, at the time of the invention, those of ordinary skill in the art recognized that different hChrs are considered substitutable in a method to produce hChr fragments and artificial chromosome vectors as per the needs of the artisan, e.g. gene of interest, disease of interest, and chromosome of interest, as successfully demonstrated by Kuroiwa (98, '00) and Tomizuka ('97).

With respect to b), as a first matter, neither Exhibits B nor C were provided in the papers filed March 25, 2009. As a second matter, those of ordinary skill in the art recognize that the common feature of all approaches to produce human artificial chromosomes is to use human α-satellite DNA to provide stable mitotic segregation function (Saffery et al), successfully demonstrated by Kuroiwa ('00). Thus, at the time of the invention, those of ordinary skill in the art would reasonably expect a human HAC comprising a deletion of a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21 to functionally achieve a degree of mitotic stability, as such a

chromosome would retain the hChr structural centromere comprising α-satellite DNA sequences having centromeric function.

10. **Claims 22, 28 and 49-50 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Kuroiwa et al (1998; *of record in IDS) in view of Kuroiwa et al (2000; *of record in IDS) and Tomizuka et al (1997; *of record in specification) and Saffery et al (2002; *of record in IDS), as applied to claims 18, 20-21, 26-27, 33 and 37-46 above, and in further view of Hattori et al (2000, *of record).

Determining the scope and contents of the prior art.

Neither Kuroiwa et al (1998, 2000), Tomizuka et al nor Saffery et al teach the wherein in step (b) the distal region of the long arm of human chromosome 21 is deleted at AL163204, and wherein the recognition site for the site- specific recombination enzyme is inserted into AL163203 in the proximal region of the long arm of human chromosome 21. However, at the time of the invention, Hattori et al taught the nucleotide sequence and annotation of human chromosome 21, achieving 99.7% coverage of 21q, within which AL163203 and AL163204 reside.

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology and the creation of transgenic cells comprising artificial/recombinant human chromosomes. Therefore, the level of ordinary skill in this art is high.

The nucleotide sequence (Accession No. AL163204) of the long-arm distal region of human chromosome 21 was obtained from the GenBank database (Specification, pg 50, ¶1).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to try substituting the insertion site of the recognition site for the site-specific recombination into AL163203 for the insertion site of Kuroiwa et al (1998, 2000) in view of Tomizuka et al and Saffery et al and the deletion of the region distal to AL163204 for the telomere truncations as per the teachings of Kuroiwa et al (1998, 2000) in view of Tomizuka et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention, and "a person of

ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." M.P.E.P. §2144.07 states "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)". When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the nucleotide sequence of human chromosome 21 was known in the prior art, and thus the ordinary artisan had access to those specific sequences necessary to design a specific telomere-truncation chromosome 21 vector comprising a specific insertion site of the recognition site for the site-specific recombination and a specific deletion of the region distal of the long and/or short arm of human chromosome 21 that retains one or more desired human chromosome 21 genes, and has removed one or more undesired human chromosome 21 genes so as to facilitate the study of the artisan's gene of interest (Hattori et al, pg 317-318, Medical Implications, Monogenic disorders, Complex Phenotypes, Neoplasias).

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that while disclosing nucleotide sequences of the human chromosome 21 that achieve 99.7% coverage of 2lq, Hattori suggests nothing about deleting a distal region within the 21ql1 region of the long arm and/or a distal region within the 21pl1 region of the short arm of the human chromosome 21.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Saffery et al teach that the strategies to produce a functional human artificial chromosome comprise the deletion of a distal region within the centromere-proximal region of the long arm and/or a distal region within the centromere-proximal region of the short arm of the human chromosome (pg 7, Figure 1; pg 9, Figure 2), whereupon the telomeric region either juxtaposes or is in close proximity to the α-satellite-based centromere.

Conclusion

11. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/

Examiner, Art Unit 1633

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